TOWARDS A PATHWAY MODELING APPROACH TO ALZHEIMER'S DISEASE DRUG DISCOVERY

Sara Ibrahim, Don Capouch, and Sujay Chandorkar
(Jake Chen, Andrew Saykin[1], Xiaogang Wu, Hui Huang),
Indiana University School of Informatics

Network pharmacology has emerged as a new topic of study in recent years. Molecular connectivity maps between drugs and genes/proteins in specific disease contexts can be particularly valuable, since the functional approach with these maps helps researchers gain global perspectives on both the therapeutic and toxicological profiles of drugs. To assess drug pharmacological effects, we assume that "ideal" drugs for a patient can treat or prevent the disease by modulating gene expression profiles of this patient to the similar level with those in healthy people. Starting from this hypothesis, we build comprehensive disease-gene-drug connectivity relationships with drug-protein directionality (inhibit/activate) information based on a computational connectivity maps (CMaps) platform. In this work, we develop a novel approach based on integrative pathway modeling. Using Alzheimer's disease (AD) as an example, we identify and rank AD-related drugs/compounds with their overall drug-protein "connectivity map" profile. First, we retrieve AD-associated proteins through the CMaps platform by using "Alzheimer's disease" as a query term. Second, we retrieve AD-related pathways by using those AD-associated proteins as input and searching in the Human Pathway Database (HPD) and the PubMed. Third, we integrate the AD-related pathways into unified pathway models, from which we categorize the pharmaceutical effects of candidate drugs on all AD-associated proteins as either "therapeutic" or "toxic" (Figure 1). Finally, we transform the integrated pathways into network models and rank drugs based on the network topological features of drug targets, drug-affecting genes/proteins, and curated AD-associated proteins. We demonstrate that our approach can help identify AD drug candidates with significant therapeutic potentials with small toxic side effects. The case study correlates very well with the existing pharmacology of AD drugs and highlights the significance of the CMaps platform. Ongoing studies towards this direction also have the potential of changing future process of AD drug development.

[1]Indiana University School of Medicine

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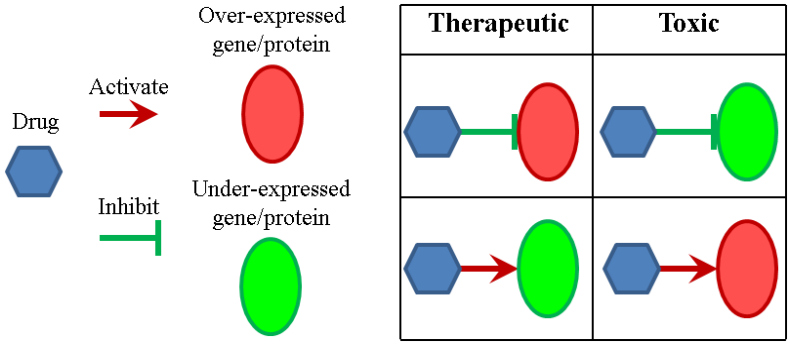
Figure 1. Illustration of drug pharmacological effects based on directionality information for drug-protein pairs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